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2,4-Dichlorophenoxyacetic Acid and Non-Hodgkin's Lymphoma, Gastric Cancer, and Prostate Cancer: Meta-analyses of the Published Literature

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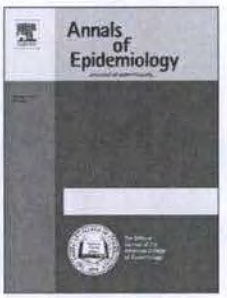

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2,4-Dichlorophenoxyacetic Acid and Non-Hodgkin's Lymphoma, Gastric Cancer, and Prostate Cancer: Meta-analyses of the Published Literature

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Abstract

Purpose: Despite evidence from experimental studies indicating that the herbicide, 2,4-dichlorophenoxyacetic acid (2,4-D), is not carcinogenic, several epidemiology studies have evaluated links between 2,4-D and cancer. Some suggest that 2,4-D is associated with non-Hodgkin's lymphoma (NHL), gastric cancer, and prostate cancer, but results have been inconsistent. We conducted meta-analyses to evaluate the weight of epidemiology evidence for these cancers.

Methods: We identified articles from PubMed, Scopus, and TOXLINE databases and reference lists of review articles. We evaluated study quality and calculated summary risk estimates using random-effects models. We conducted subgroup and sensitivity analyses when possible.

Results: We identified nine NHL, three gastric cancer, and two prostate cancer studies for inclusion in our meta-analyses. We found that 2,4-D was not associated with NHL (RR = 0.97, 95% CI = 0.77-1.22, I^2 = 28.8%, $p_{heterogeneity}$ = 0.19) and this result was generally robust to subgroup and sensitivity analyses. 2,4-D was not associated with gastric (RR = 1.14, 95% CI = 0.62-2.10, I^2=54.9%, $p_{heterogeneity}$ = 0.11) or prostate cancer (RR = 1.32, 95% CI = 0.37-4.69, I^2 87.0%, $p_{heterogeneity}$ = 0.01).

Conclusions: The epidemiology evidence does not support an association between 2,4-D and NHL, gastric cancer, or prostate cancer risk.

Keywords:
2,4-D, cancer, non-Hodgkin's lymphoma, gastric cancer, prostate cancer, meta-analysis, systematic review, epidemiology

List of Abbreviations

2,4-D – 2,4-dichlorophenoxyacetic acid;
AHS – Agriculture Health Study;
CI – confidence interval;
I^2 – I-squared Statistic
IARC – International Agency for Research on Cancer;
NHL – non-Hodgkin's lymphoma;
OR – odds ratio;
RR – relative risk;
SIR – standardized incidence ratio;
SMR – standardized mortality ratio;
US EPA – United States Environmental Protection Agency.

Introduction

2,4-Dichlorophenoxyacetic acid (2,4-D) is a chlorophenoxy herbicide that was developed in the 1940s to selectively control broadleaf weeds in agriculture. Currently, annual usage ranks first and seventh among herbicides in residential and agricultural markets, respectively (US EPA, 2011). 2,4-D has a half-life in the environment of 2-13 days (Wilson *et al.*, 1997), and it is cleared quickly from the human body without being metabolized or accumulating in tissue (Saghir *et al.*, 2013).

In 1987, the International Agency for Research on Cancer (IARC) classified chlorophenoxy herbicides as "possible carcinogens" but did not evaluate 2,4-D specifically (IARC, 1987). Several regulatory agencies in the US, Canada, and Europe independently assessed the scientific evidence and have concluded that research does not support a causal relationship between 2,4-D exposure and cancer (European Commission, 2001, 2014; US EPA, 2005; Health Canada, 2008).

Despite this, a number of epidemiology studies have evaluated 2,4-D and cancer and reported mixed results. To our knowledge, the only meta-analysis of these studies was conducted by Schinasi and Leon (2014), who carried out 40 meta-analyses of non-Hodgkin's lymphoma (NHL) and 21 pesticide chemical groups and 80 active ingredients. The authors reported a marginally significant elevation of NHL associated with 2,4-D exposure (summary relative risk [RR] = 1.34, 95% confidence interval [CI] = 1.03-1.91), but certain study limitations undermined the validity of the results. In addition, there is some epidemiology evidence suggesting positive associations between 2,4-D exposure and gastric and prostate cancer (Mills and Yang, 2007; Band *et al.*, 2011). To our knowledge, there have been no published meta-analyses evaluating 2,4-D and these two cancers.

In this study, we systematically reviewed the literature and conducted meta-analyses to determine whether 2,4-D epidemiology studies support associations with NHL, gastric cancer, or prostate cancer risk.

Methods

Literature Search

We searched PubMed, Scopus, and TOXLINE databases for peer-reviewed observational epidemiology studies evaluating 2,4-D and NHL, gastric cancer, or prostate cancer published through October 9, 2014, using the following search terms: "(2,4-dichlorophenoxyacetic acid OR 2,4-d) AND (cancer OR carcinogenesis OR carcinogenicity OR carcinogenic OR tumors OR neoplasms OR lymphoma)." We also searched bibliographies of recent review articles on 2,4-D and cancer to identify additional relevant publications.

Study Selection

We included peer-reviewed observational studies that evaluated associations between 2,4-D and NHL, gastric cancer, and prostate cancer in adult humans. We excluded animal and *in vitro* studies; studies that did not specifically evaluate 2,4-D exposure alone; studies that did not evaluate NHL, gastric cancer, or prostate cancer; review articles; commentaries; and editorials.

We included studies that reported quantitative risk estimates specifically associated with 2,4-D exposure in the meta-analysis. We excluded one ecological study. Whenever there were multiple publications describing the same population, we selected the most recent study that considered or adjusted for potential exposures to other pesticides.

Two investigators (K.Z., C.L.) independently reviewed each study for inclusion, first by reviewing titles and abstracts, and then the full text. When there was a disagreement, the study was discussed until consensus was achieved.

Data Extraction

We extracted information from each study on the study location, population from which cases arose, numbers of cases and non-cases, years of case identification, age and sex of subjects, and exposure type (*i.e.*, agricultural, industrial, other occupational, or residential). We also extracted information on study design, exposure ascertainment, exposure metrics, whether dose-response patterns were assessed, outcome ascertainment, confounders considered, and whether sensitivity analyses were conducted.

We extracted risk estimates and 95% CIs for all 2,4-D exposure categories reported. The risk estimates included standardized incidence ratios (SIRs) and standardized mortality ratios (SMRs) from cohort studies, and odds ratios (ORs) from case-control studies. We also extracted p-values for trend tests when provided. When quantitative results necessary for meta-analysis were not presented, we contacted the authors for data.

Two investigators (K.Z., C.L.) independently extracted qualitative and quantitative information using a standardized data extraction form. When there was a discrepancy, the two investigators discussed and resolved the inconsistency.

Statistical Analysis

We conducted separate meta-analyses for NHL, gastric cancer, and prostate cancer using Stata version 13.1 (StataCorp LP; College Station, TX). All risk estimates and CIs extracted from original studies were log-transformed prior to analysis. Random effects models were chosen *a priori* over fixed effects models because of the heterogeneity among study designs and populations, as well as the variability in the 2,4-D exposures. We repeated all analyses using fixed effects models in sensitivity analyses and found that the summary RR did not change by more than 10% in any case. We only present results from random effects models. To assess the degree of between-study heterogeneity in each analysis, we used the I-squared (I^2) statistic and associated p-value from a chi-square test.

For NHL, we calculated a pooled RR for dichotomous 2,4-D exposure. We also conducted subgroup analyses to explore potential sources of heterogeneity. Subgroups were chosen *a priori* and included study design (cohort or nested case-control *vs.* population-based case-control), type of exposure (exclusively agricultural *vs.* other), location (US *vs.* non-US), and sex (male *vs.* both sexes). We also conducted sensitivity analyses based on several variations in study inclusion, and repeated analyses in which each study was excluded in turn to test whether results are sensitive to inclusion of any single study. Finally, to assess potential publication bias, we constructed a funnel plot of the log RR *vs.* its standard error and visually inspected the plot; we also conducted Begg's and Egger's tests (Begg and Mazumdar, 1994; Egger *et al.*, 1997).

We identified only three gastric cancer and two prostate cancer studies that reported quantitative results appropriate for inclusion in our meta-analyses. Therefore, we did not perform subgroup analyses, sensitivity analyses, or a publication bias assessment for these endpoints.

Results

Study Selection

Through online database searches and cross-referencing of works cited in recent reviews (Burns and Swaen, 2012; von Stackelberg, 2013; Schinasi and Leon, 2014), we identified 293 potentially relevant publications (Figure 1). Based on titles and abstracts, we identified 42 studies for full-text review. We further excluded 18 studies because they met one of our exclusion criteria. We identified 24 studies for systematic review; of these, nine were included in the NHL meta-analysis, three in the gastric cancer meta-analysis, and two in the meta-analysis of prostate cancer. We contacted the investigators of the Agricultural Health Study (AHS) in an attempt to obtain quantitative results on 2,4-D and NHL, gastric, and prostate cancer, but we did not receive a response.

Overview of Epidemiology Studies

Of 24 relevant epidemiology studies (Table 1), the majority are case-control and focused on exposures from agricultural work (*e.g.*, while applying pesticides or working in fields where pesticides were applied). Three of the studies were conducted in different states across the Midwestern US and assessed NHL risk (Hoar *et al.*, 1986; Cantor *et al.*, 1992; Zahm *et al.*, 1990). De Roos *et al.* (2003) pooled results from these three studies in a subsequent analysis that accounted for co-exposures to other pesticide active ingredients. A subset of the Nebraska study (Zahm *et al.*, 1990) was additionally analyzed for incidence of gastric cancer (Lee *et al.*, 2004).

A series of publications involving the United Farm Workers of America cohort in California included an ecological study of NHL and regional pesticide applications (Mills, 1998) and nested case-control studies of NHL (Mills *et al.*, 2005) and gastric cancer (Mills and Yang, 2007). Other agricultural investigations included a study by Woods and Polissar (1989), who evaluated a population-based case-control study of NHL in farm workers in Washington State, and a prospective cohort study conducted by Alavanja *et al.* (2003), who analyzed prostate cancer incidence in ~55,000 pesticide applicators in the AHS cohort. Studies of agricultural exposures outside the US include the Italian Case-control Study on Hematolymphopoietic Malignancies (Miligi *et al.*, 2003, 2006) and a proportional registration study of prostate cancer incidence in Canada (Band *et al.*, 2011).

Another occupational exposure setting we reviewed was a pesticide manufacturing plant in Michigan. A cohort of 2,4-D production plant workers was followed over several decades for several cancers, including NHL, gastric, and prostate cancers. Analyses of cancer mortality were reported by Bond *et al.* (1988), Bloemen *et al.* (1993), and Burns *et al.* (2001). The most current analysis of this cohort was conducted by Burns *et al.* (2011), who assessed cancer incidence.

Several studies involved subjects who were exposed to 2,4-D under less specific conditions. McDuffie *et al.* (2001), Hohenadel *et al.* (2011), and Pahwa *et al.* (2012) reported findings from the Cross-Canada Study of Pesticides and Health, a population-based case-control study of NHL incidence. Only about half of the men in this population ever resided on a farm, and 2,4-D exposure included agricultural and "home, garden, or hobby" uses. Hardell *et al.* (1994) and Kogevinas *et al.* (1995) described two separate European case-control investigations of NHL and occupational exposures, including those experienced in

agriculture and other occupations, such as railway work. Hartge *et al.* (2005) focused specifically on residential exposures in carpet dust in a case-control study of NHL in Washington State.

Study Quality Assessment

We assessed several study quality characteristics in our systematic review (Table 2). Only five of 24 studies were cohort studies. There were three nested and 14 population-based case-control studies. We identified one ecological and one proportional registration ratio study; these studies are of lower quality than case-control and cohort studies.

The most common method of outcome ascertainment was through the use of cancer registries, hospital records, and/or death certificates. Although this approach is susceptible to misclassification, 12 investigations included pathology review of suspected cases, which increased the accuracy. In addition, diagnosis and classification of NHL have changed and improved over time (Hartge *et al.*, 1994; NCI, 2015), and this likely led to errors in outcome ascertainment in epidemiology studies of 2,4-D and NHL.

Approaches for exposure assessment were similar across studies, with the majority relying on self- and proxy-report of 2,4-D exposure, using written questionnaires, phone interviews, or in-person interviews, generally years or decades following the period of exposure. In several studies, self-reported exposure histories were augmented by use of job or crop exposure matrices (n = 6) or pesticide supplier records (n = 1), which may have improved accuracy. Hartge *et al.* (2005) took environmental measurements in subjects' homes at the time of outcome assessment; this may not have accurately reflected exposures during etiologically relevant time periods. Exposure assessment in four analyses of the Dow cohort was based on company employment records and job exposure matrices informed by industrial hygiene measurements of 2,4-D in workplaces. This method is less susceptible to inaccuracies, but errors and uncertainties in job exposure matrices could affect the validity of exposure estimates. The majority of the studies categorized exposure to 2,4-D using dichotomous metrics such as yes *vs.* no, ever *vs.* never, or high *vs.* low. Ten studies evaluated other exposure metrics in addition to these, though only five conducted a trend test to assess dose-response.

Many approaches were used to address confounding. All studies with individual-level data adjusted for age, and all with both males and females adjusted for sex. Other covariates were smoking, geographic location/study site, respondent type (proxy *vs.* self), alcohol consumption, year, race, income, vital status, family history of cancer, and general medical history. Notably, only three studies accounted for co-exposure to pesticides containing other active ingredients (De Roos *et al.*, 2003; Mills *et al.*, 2005; Hohenadel *et al.*, 2011). In general, consideration of potential confounders appears limited and inconsistent in these studies, and results of many studies may have been affected by unmeasured or residual confounding.

Finally, only a small number of studies conducted sensitivity analyses, including variations in cohort definition (n = 1), restriction of the study population (n = 1), and latency analyses using lagged exposures (n = 3). Also, several studies analyzed many exposures and outcomes, creating a possible "multiple comparison problem" (dos Santos Silva, 1999); none of the studies accounted for this.

Non-Hodgkin's Lymphoma

We identified 19 studies evaluating 2,4-D and NHL (Supplemental Table 1). Seventeen presented risk estimates, and 11 reported null associations across all analyses. Four reported a statistically significant elevation of risk in main analyses, and two reported elevated risks in an exploration of subgroups.

A limited number of investigations explored dose-response among three or more categories of exposure, quantified as duration of employment (Burns *et al.*, 2011), cumulative exposure (Burns *et al.*, 2001, 2011, Kogevinas *et al.*, 1995), categories of 2,4-D concentration in carpet dust (Hartge *et al.*, 2005), or frequency of exposure (Zahm *et al.*, 1990, McDuffie *et al.*, 2001). The results were overwhelming null for risk estimates pertaining to individual categories of exposure compared to lowest exposure, as well as when trends across increasing categories were tested. Exceptions include select dose-response results presented by Zahm *et al.* (1990). They reported a statistically significant elevation of risk in a single category of exposure duration (OR = 2.8, 95% CI = 1.1-7.1, for 6-16 years of exposure compared to never exposed); however, a statistical test of trend across all categories was not significant (p = 0.274). They also reported a borderline significant test of trend across increasing frequency of exposure, measured as days per year (p = 0.051), and an increasing trend in NHL risk for workers who reported waiting longer to change clothes after handling pesticides (p = 0.015), but this was based on very small numbers of cases per category. Burns *et al.* (2011) observed a suggestive but non-statistically significant elevated risk in the highest category of employment duration (RR = 3.08, 95% CI = 0.84-7.88; $p_{trend} = 0.12$); however, a dose-response assessment of cumulative exposure yielded null results ($p_{trend} = 0.46$).

We included nine studies in the meta-analysis. We excluded one ecological study (Mills, 1998) and eight studies that were superseded by more recent publications of the same study populations (Burns *et al.*, 2001; Bloemen *et al.*, 1993; Miligi *et al.*, 2003; McDuffie *et al.*, 2001; Zahm *et al.*, 1990; Weisenberger, 1990; Cantor *et al.*, 1992; Hoar *et al.*, 1986). Results of the excluded ecological study were null, and results of the superseded studies were similar to updated analyses in all cases. We also preferentially selected adjusted risk estimates whenever possible. We selected the pooled RR reported by De Roos *et al.* (2003) instead of individual results from Cantor *et al.* (1992), Hoar *et al.* (1986), and Zahm *et al.* (1990) because De Roos *et al.* (2003) adjusted for exposure to other pesticides. Likewise, Hohenadel *et al.* (2011) was included in our primary meta-analysis instead of Pahwa *et al.* (2012) because, even though it was an older publication, Hohenadel *et al.* (2011) accounted for exposure to other pesticides in the analysis.

Our primary meta-analysis yielded a summary RR of 0.97 (95% CI = 0.77-1.22) (Figure 2). Two studies contributed the most weight (Hohenadel *et al.*, 2011; De Roos *et al.*, 2003), both of which had individual risk estimates slightly below 1, though neither was statistically significant. The two studies reporting the most elevated point estimates (Mills *et al.*, 2005; Hardell *et al.*, 1994) were assigned the lowest weights. Based on an I^2 of 28.8% (p = 0.189), there was a low-to-moderate degree of between-study heterogeneity.

We explored whether the results of our primary analysis varied by study characteristics (Table 3). Summary RRs did not appear to vary by the type of exposure, geographic location, sex of subjects, or whether exposure to other pesticides was adjusted for in the analysis. Three cohort/nested case-control studies yielded a non-significant meta-RR of 1.49, while population-based case-control studies yielded null results. However, despite a more robust study design, these three studies suffered similar limitations as case-control studies, such as exposure measurement error and confounding. Our confidence in this elevated risk estimate is further limited by the small number of studies and the possibility that multiple comparisons across several sets of subgroups led to spurious associations.

In sensitivity analyses, we evaluated whether several variations in the selection of studies and/or risk estimates affected results (Table 4). The summary RR was robust to the majority of variations on study/risk estimate selection, including systematic exclusion of each study individually. We observed a small, marginally significant elevation in NHL risk when we preferentially selected all risk estimates that were unadjusted for other pesticide exposure (RR = 1.34, 95% CI = 1.04-1.72); however, the results displayed considerable between-study heterogeneity ($I^2 = 56.3\%$, $p_{heterogeneity} = 0.011$).

The funnel plot for our primary NHL analysis (Figure 3) indicated possible publication bias, with an over-representation of small studies reporting positive associations. Two statistical tests of publication bias supported this finding (p = 0.018 and 0.076 for Egger's and Begg's tests of small study effects, respectively).

Gastric Cancer

We identified four studies reporting risk estimates for gastric cancer (Supplemental Table 2). Only one (Mills and Yang, 2007) estimated risks across several categories of exposure, quantified as annual pounds of 2,4-D use. An elevated OR was associated with the second-lowest category of exposure relative to no exposure (OR = 2.16, 95% CI = 1.02-4.56), but point estimates in the third and fourth quartiles were lower than that of the second quartile, and in neither case were the ORs statistically significant. The authors did not report results of a trend test.

We excluded Bond *et al.* (1988) because it was superseded by Burns *et al.* (2011), and included three studies in our meta-analysis. The summary RR was 1.14 with a 95% CI of 0.62-2.10 (Figure 4), with relatively large weights assigned to Mills and Yang (2007) and Lee *et al.* (2004). There was evidence of considerable between-study heterogeneity (I^2 = 54.9%, $p_{heterogeneity}$ = 0.109).

Because of the small number of studies, we did not assess publication bias.

Prostate Cancer

We identified five studies that evaluated prostate cancer (Supplemental Table 3). We excluded Bond *et al.* (1988) and Burns *et al.* (2001) from the meta-analysis because they were superseded by Burns *et al.* (2011), and Alavanja *et al.* (2003) because it did not report risk estimates (Alavanja *et al.*, 2003). The remaining two studies reported statistically significant associations with prostate cancer risk in opposing directions, and we calculated a summary RR of 1.32 (95% CI = 0.37-4.69) associated with 2,4-D exposure (Figure 5).

The three studies excluded from the meta-analysis all reported null associations between 2,4-D and prostate cancer (Bond *et al.*, 1988; Burns *et al.*, 2001; Alavanja *et al.*, 2003). None of the studies estimated exposure across more than two categories, so no dose-response information is available.

Because of the small number of studies, we did not assess publication bias.

Discussion

Our systematic review and meta-analyses indicate that epidemiology evidence does not support an association between 2,4-D exposure and NHL, gastric cancer, or prostate cancer. For NHL, we found that meta-results were generally robust to several subgroup and sensitivity analyses, with a single exception (discussed below). Our meta-analyses did not incorporate results from the dose-response analyses that were conducted in a limited number of NHL studies. However, results of dose-response analyses were largely null and consistent with our meta-analysis findings. In addition, results of individual studies that we excluded from the meta-analysis were consistent with those from studies we included.

Our findings are consistent with the conclusions of other recent reviews. Burns and Swaen (2012) reviewed recent epidemiology research and determined that there is inconsistent evidence regarding increased risks of NHL or other cancers of the lymphatic system. Similarly, von Stackelberg (2013) systematically reviewed epidemiology, toxicology, pharmacokinetic, exposure, and biomonitoring studies to assess the potential carcinogenicity of 2,4-D and reported that epidemiology evidence with regard to 2,4-D and cancer is mixed, and that the proposed mechanisms for a causal relationship require exposure and dose concentrations that far exceed any realistic exposure scenarios.

The lack of associations between 2,4-D and cancer outcomes in our analyses is also well supported by several decades of toxicology research (*e.g.*, see reviews by Burns and Swaen, 2012; Garabrant and Philbert, 2002). For example, rodent oncogenicity studies that covered a wide range of dose levels of 2,4-D clearly establish no-observable-adverse-effect levels and maximum tolerated doses for chronic toxicity (Munro *et al.*, 1992; Charles *et al.*, 1996). There was some initial concern over a non-statistically significant increase in male rat astrocytomas at 45 mg/kg-day in the earlier rat study. However, a subsequent study conducted with doses of 75 and 150 mg/kg-day (Charles *et al.*, 1996), and the non-linear toxicokinetics of 2,4-D due to saturation of renal clearance (Gorzinski *et al.*, 1987; van Ravenzwaay *et al.*, 2003; Saghir *et al.*, 2013), indicate that this was a spurious finding bearing no relationship to treatment (Munro *et al.*, 1992).

It is also notable that pharmacokinetic and biomonitoring studies of 2,4-D indicate that doses experienced by humans, even in the most extreme occupational exposure scenarios, are orders of magnitude lower than reference concentrations established from toxicology studies (Aylward *et al.*, 2010; Burns and Swaen, 2012).

Three common modes of action (MoAs) have been proposed for 2,4-D carcinogenicity: genotoxicity, immunotoxicity, and endocrine or receptor-mediated processes. The weight of evidence shows that 2,4-D is not genotoxic *in vitro* or *in vivo* (Burns and Swaen, 2012; Charles *et al.*, 1999a,b; Rowland, 1996; Dole and Taylor, 2004; US EPA, 2013; EFSA, 2014; European Commission, 2001; Gollapudi *et al.*, 1999; New Zealand Pesticides Board, 2000; Health Canada, 1991, 2007; von Stackelberg, 2013; FAO and WHO, 1996). Although a transient, short-term immunomodulatory effect of 2,4-D in humans was reported in a single preliminary study (Faustini *et al.*, 1996), other more robust studies indicate that 2,4-D is not immunotoxic or immunosuppressive (Blakley *et al.*, 1992, 1998; Carlo *et al.*, 1992; Charles *et al.*, 1996; Garabrant and Philbert, 2002; Kaneene and Miller, 19995; Marty *et al.*, 2013; US EPA, 2012). Finally, numerous studies have been conducted to assess the potential for interactions with the endocrine system, including studies conducted for the US EPA Endocrine Disruptor Screening Program (EDSP), and an extended one-generation reproductive toxicity study that serves as Tier II/OECD Level 5 definitive data. These studies demonstrate that 2,4-D does not alter estrogen receptor activity *in vitro* or *in vivo*

(Coady *et al.*, 2013; Marty *et al.*, 2013; Sun *et al.*, 2012). Taken together, the weight of evidence indicates that there is no plausible carcinogenic MoA for 2,4-D.

In contrast to our findings, Schinasi and Leon (2014), who conducted a series of meta-analyses of 21 pesticide chemical groups and 80 active ingredients and NHL, reported a marginally significant summary RR of 1.4 (95% CI = 1.0-1.9) associated with high 2,4-D exposure, compared to relatively low exposure based on five original studies reviewed here: Zahm *et al.* (1990), Cantor *et al.* (1992), Mills *et al.* (2005), Miligi *et al.* (2006), and Pahwa *et al.* (2012). Schinasi and Leon (2014) indicated that they restricted their analyses to occupational agricultural exposure to 2,4-D; however, one study evaluated both occupational and non-occupational exposures (Pahwa *et al.*, 2012) and should have been excluded from the meta-analyses according to their inclusion criteria. The validity of their meta-estimate is further challenged by a high degree of between-study heterogeneity, as indicated by an I^2 of 61.5%, that was not explained by exploratory subgroup analyses. Schinasi and Leon (2014) conducted limited sensitivity analyses based on variations in study selection, but they did not discuss or explain why the association between 2,4-D and NHL became nonsignificant when pooled RRs from De Roos *et al.* (2003) were selected in place of the individual results from Hoar *et al.* (1986), Zahm *et al.* (1990), and Cantor *et al.* (1992). It should also be noted that the authors calculated 40 meta-risk estimates from 44 publications based on 17 original studies, so some of their statistically significant findings are likely attributable to chance.

Strengths of our approach include a thorough evaluation of study quality and a rigorous approach to subgroup and sensitivity analyses for NHL, the only endpoint with sufficient sample size to allow for these analyses. In contrast to Schinasi and Leon (2014), who focused on agricultural 2,4-D exposures exclusively, we considered epidemiology studies of exposures in a wide variety of occupational scenarios and during non-occupational 2,4-D use. Because of the substantial heterogeneity in 2,4-D exposure experienced across these disparate settings, we conducted subgroup analyses to explore whether meta-estimates varied between exposure types (*i.e.*, agricultural, industrial, and other). Our statistical test of between-group heterogeneity revealed no evidence of effect modification by exposure type, although this test may have been underpowered to detect true differences. Each NHL meta-analysis we conducted included up to 13 effect estimates, compared to only five in the meta-analysis by Schinasi and Leon (2014). An additional distinction between approaches is that we placed more confidence in the validity of risk estimates adjusted for pesticide co-exposures and preferentially selected risk estimates adjusted for other pesticides whenever possible. The result of our sensitivity analysis in which risk estimates unadjusted for other pesticides were selected is nearly identical to the results of Schinasi and Leon (2014).

Besides Schinasi and Leon (2014), the only other relevant meta-analysis we identified is that by Morrison *et al.* (1992), which was conducted prior to the publication of many of the epidemiology studies and was an evaluation of chlorophenoxy herbicides as a broad class of chemicals and not 2,4-D specifically. To our knowledge, our meta-analysis of 2,4-D is the most thorough analysis conducted to date, and our meta-analyses of gastric and prostate cancers, while small in size, are the first to be reported in the published literature.

Despite several strengths of our approach, it has a few potential limitations. Because there are so few NHL epidemiology studies, all of our statistical tests of subgroup heterogeneity and publication bias conducted for NHL are likely under-powered and should be considered highly exploratory in nature. Meta-analyses of gastric and prostate cancers included only three and two studies, respectively. Another limitation to be considered is that the validity of a meta-analysis depends on the validity of the individual risk estimates extracted from underlying epidemiology studies. We identified methodological limitations in each epidemiology study that may have biased associations and increased the uncertainty of meta-analysis results.

Most studies we reviewed are case-control in design with relatively small sample sizes. In contrast, the AHS study is a long-term prospective cohort study of over 52,000 pesticide applicators, whose exposure to 2,4-D was assessed by questionnaire. We did not include AHS results in our meta-analysis because evaluations of NHL, gastric cancer, and prostate cancer have either not been peer-reviewed (NHL, gastric cancer) or included quantitative results (prostate cancer). Beane Freeman *et al.* (2013) described analyses of 2,4-D and NHL and gastric cancer risk in an abstract submitted to the 24th International Epidemiology in Occupational Health Conference. The authors estimated gastric cancer risk across quartiles of 2,4-D exposure and found that estimated risk in the highest quartile of 2,4-D exposure was elevated relative to the lowest quartile (RR = 2.3, 95% CI = 1.1-5.2, p_{trend} across quartiles = 0.03) (Beane Freeman *et al.*, 2013). We evaluated whether inclusion of this result would affect our results. Specifically, we repeated the gastric cancer meta-analysis including the risk estimate for the highest quartile in Beane Freeman *et al.* (2013) to represent a RR for the high exposure group, and found that the summary RR was still null (RR = 1.34, 95% CI = 0.78-2.30, I^2 = 55.1, $p_{heterogeneity}$ = 0.083). Including the RR for the highest quartile of exposure likely overestimated the summary RR for dichotomous exposure and reduced the precision.

Beane Freeman *et al.* (2013) also reported that the association between NHL and 2,4-D in the AHS cohort was null, but they did not present quantitative risk estimates. Analyses of prostate cancer incidence in the AHS have been published in the peer-reviewed literature (Alavanja *et al.*, 2003), but associations with 2,4-D were described only as being nonsignificant; no quantitative findings were provided. Because of the null results reported in the AHS study, inclusion of this study into our meta-analyses of NHL and prostate cancer would have increased the precision of the summary RRs but would not likely change the overall null associations. Also, the unreported null results from the AHS cohort support our assessment of publication bias that small studies with positive associations may be over-represented in the epidemiology literature of 2,4-D and NHL.

Perhaps the largest methodological limitation of 2,4-D epidemiology studies pertains to exposure assessment. In most cases, 2,4-D use was evaluated through interviews or by questionnaires, and there may have been substantial error in exposure assessment. For example, Hoar *et al.* (1986) only inquired about herbicide use (instead of 2,4-D specifically) in their questionnaire but reported results for 2,4-D based on study participants' claims that they were using 2,4-D. In addition, 2,4-D exposure was estimated based on subjective recall of past exposure by subjects and proxy respondents. Accuracy of self- and proxy reports is compromised by imperfect recollection of events that occurred many years or decades in the past, and cancer patients may be more likely to report prior use of pesticides than control subjects. In addition, in some studies, the proportion of exposure questionnaires completed by proxy respondents varied between cases and controls. For example, Miligi *et al.* (2003) collected exposure information from proxies for only 4% of control subjects but 23% of cases, while most other researchers did not explicitly note these proportions. Differences in type of respondent between cases and controls is important because some 2,4-D studies demonstrated that exposure estimates varied by respondent type. Lee *et al.* (2004) found that proxy respondents were more likely to provide "don't know" responses, and self-respondents were more likely to report pesticide exposure than proxies. Likewise, Cantor *et al.* (1992) observed that proxy respondents were approximately five times more likely to respond "don't know" to questions about 2,4-D exposure than self-respondents. Zahm *et al.* (1990) reported that risk estimates for NHL associated with 2,4-D handling was nearly twice as high when analysis was restricted to subjects with proxy interviews compared to self-respondents. Therefore, in the 2,4-D epidemiology studies, the impact of information bias may be substantial.

Finally, it is difficult to interpret risk estimates associated with 2,4-D exposure in light of the strong possibility of co-exposures highly correlated with 2,4-D. Farm workers are commonly exposed to a large number of agricultural compounds, including assorted herbicides, insecticides, and fungicides, and some workers in the Dow manufacturing cohort were exposed to benzene, asbestos, and other potentially carcinogenic compounds (Burns *et al.* 2011). Despite the probability of important co-exposures, few 2,4-

D epidemiology studies adjusted for exposure to other chemical agents; those that did demonstrated that adjustment almost always attenuated risk estimates. We chose to prioritize risk estimates adjusted for other pesticides in our NHL meta-analysis. In sensitivity analyses of the NHL meta-analysis, the only statistically significant meta-estimate we observed resulted from a preferential selection of individual risk estimates without adjustment for pesticide co-exposures. We believe this finding suggests that observed associations between 2,4-D and cancer are often confounded by other factors.

In conclusion, we systematically reviewed all available epidemiology evidence relevant to 2,4-D exposure and NHL, gastric cancer, and prostate cancer, and quantitatively synthesized results from 12 published studies. The meta-analyses had increased statistical power over individual studies, yet we found no associations overall between 2,4-D and any cancer endpoint. The validity of our meta-estimates is limited by uncertainties and potential biases in results of individual studies, but considered with the large, robust database of toxicology research and pharmacokinetic and human biomonitoring studies, the weight of evidence does not support causal relationships between 2,4-D exposure and NHL, gastric cancer, or prostate cancer.

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Legends:

Figure 1: Selection of studies for systematic review and meta-analyses of 2,4-D and NHL, gastric cancer, and prostate cancer.

Figure 2: Forest plot of study-specific and summary RRs with 95% CIs for NHL. Studies were pooled using a random effects model. Squares represent study-specific risk estimates and the size of each square is proportional to the study-specific statistical weight. The horizontal lines show 95% CIs for study-specific estimates. The diamond represents the summary risk estimate and its corresponding 95% CI.

Figure 3: Funnel plot of NHL RRs associated with 2,4-D exposure. The log of risk estimates *versus* log of risk estimate standard errors for each individual study are plotted. The red line represents the fitted regression test for funnel-plot asymmetry.

Figure 4: Forest plot of study-specific and summary RRs with 95% CIs for gastric cancer. Studies were pooled using a random effects model. Squares represent study-specific risk estimates and the size of each square is proportional to the study-specific statistical weight. The horizontal lines show 95% CIs for study-specific estimates. The diamond represents the summary risk estimate and its corresponding 95% CI.

Figure 5: Forest plot of study-specific and summary RRs with 95% CIs for prostate cancer. Studies were pooled using a random effects model. Squares represent study-specific risk estimates and the size of each square is proportional to the study-specific statistical weight. The horizontal lines show 95% CIs for study-specific estimates. The diamond represents the summary risk estimate and its corresponding 95% CI.

Table 1 General Characteristics of Studies Evaluating 2,4-D and NHL, Gastric Cancer, and Prostate Cancer

Study	Outcomes assessed	Location	Study Population	# of Cases	# of Non-cases	Years of Case Identification	Age	Sex	Exposure Type
Cohort Studies[a]									
Burns *et al.* (2011)	NHL, gastric cancer, and prostate cancer	Michigan, US	Chemical workers (the Dow cohort)	14	1,242	1985-2007	19 - >70	M	Industrial
Alavanja *et al.* (2003)	prostate cancer	Iowa, North Carolina, US	Pesticide applicators (the AHS[b] cohort)	566	54,766	1993-1999	NR	M	Agricultural
Burns *et al.* (2001)	NHL, prostate cancer	Michigan, US	Chemical workers (the Dow cohort)	3	1,564	1945-1994	<25 - ≥45	M	Industrial
Bloemen *et al.* (1993)	NHL	Michigan, US	Chemical workers (the Dow cohort)	2	876	1945-1986	NR	M	Industrial
Bond *et al.* (1988)	gastric cancer, prostate cancer	Michigan, US	Chemical workers (the Dow cohort)	1	878	1945-1982	Mean = 28.7 at entry	M	Industrial
Nested Case-control Studies									
Mills and Yang (2007)	Gastric cancer	California, US	Farm workers (the UFWA Cohort)	100	210	1988-2003	NR	M, F	Agricultural
Mills *et al.* (2005)	NHL	California, US	Farm workers (the UFWA[c] Cohort)	60	300	1987-2001	NR	M, F	Agricultural
Kogevinas *et al.* (1995)	NHL	Australia and European countries[d]	Chemical workers and sprayers (the IARC[e] cohort)	32	158	NR	NR	M, F	Agricultural & industrial
Population-based Case-control Studies									

Pahwa *et al.* (2012)	NHL	Canada	Adult men	513	1,506	1991-1994	Cases: 58 ± 14 Controls: 54 ± 16	M	Agricultural & other
Hohenadel *et al.* (2011)	NHL	Canada	Adult men	513	1,506	1991-1994	≥19	M	Agricultural & other
Miligi *et al.* (2006)	NHL	Italy	Adults	1,145[f]	1,232	1991-1993	20 - 74	M, F	Agricultural
Hartge *et al.*(2005)	NHL	Iowa, Los Angeles, Detroit, Seattle, US	Adults	679	510	1998-2000	20 - 74	M, F	Residential
Lee *et al.* (2004)	Gastric cancer	Nebraska, US	Adult men	170	502	1988-1993	≥21	M, F	Agricultural
De Roos *et al.* (2003)	NHL	Nebraska, Iowa, Minnesota, Kansas, US	Adult men	650	1,933	1979-1986	≥21	M	Agricultural
Miligi *et al.* (2003)	NHL	Italy	Adult	1,145[f]	1,232	1991-1993	20 - 74	M, F	Agricultural
McDuffie *et al.* (2001)	NHL	Canada	Adult men	517	1,506	1991-1994	Cases: 57.7 ± 14 Controls: 55.0 ± 16	M	Agricultural & other
Hardell *et al.* (1994)	NHL	Sweden	Adult men	105	335	1974-1978	25 - 85	M	Other
Cantor *et al.* (1992)	NHL	Iowa, Minnesota, US	Adult men	622	1245	1980-1983	≥30	M	Agricultural
Zahm *et al.* (1990)	NHL	Nebraska, US	Adult men	201	725	1983-1986	≥20	M	Agricultural
Weisenberger (1990)	NHL	Nebraska, US	Adult men	201	725	1983-1987	≥21	M	Agricultural
Woods and Polissar (1989)	NHL	Washington, US	Adult men	181	196	1981-1984	20 - 79	M	Agricultural
Hoar *et al.* (1986)	NHL	Kansas, US	Adult men	170	948	1979-1981	≥21	M	Agricultural
Proportional Registration Ratio Study									
Band *et al.* (2011)	Prostate cancer	Canada	Adult men	1,153	3,999	1983-1990	Cases: 70.9 ± 8.0 Controls: 66.9 ± 9.2	M	Agricultural
Ecological Study									
Mills (1998)	NHL	California, US	Adult	NR	NR	1988-1992	NR	M, F	Agricultural

Notes:

NHL - non-Hodgkin's lymphoma; M - male; F - female; NR - not reported.

(a) All of the cohort studies were retrospective, except for Alavanja et al. (2003), which was prospective.

(b) AHS for Agricultural Health Study.

(c) UFWA for United Farm Workers of America.

(d) Australia, Denmark, Finland, Germany, the Netherlands, New Zealand, Sweden, and the United Kingdom.

(e) IARC for International Agency for Research on Cancer.

(f) Includes both NHL and chronic lymphocytic leukemia (CLL).

Table 2 Methods of Studies Evaluating 2,4-D and NHL, Gastric Cancer, and Prostate Cancer

Study	Study Design	Exposure Measurement[a]	Exposure Metrics[b]	Dose Response[c]	Outcome Ascertainment	Confounders Considered[d]					Sensitivity Analysis
						Age	Sex	Family history	Other pesticides	Other	
Burns *et al.* (2011)	Cohort	Company record/JEM	D, L, C	Yes	Cancer registry	√					Different cohort definitions
Alavanja *et al.* (2003)	Cohort	Self report	F, L, I, C	No	Cancer registry, death certificate	√		√			None
Burns *et al.* (2001)	Cohort	Company record/JEM	D, C	Yes	Death certificate	√				√	Latency analyses
Bloemen *et al.* (1993)	Cohort	Company record/JEM	D	No	Death certificate	√				√	None
Bond *et al.* (1988)	Cohort	Company record/JEM	D, L, C, TF	No	Death certificate	√					Latency analyses
Mills and Yang (2007)	Nested case-control	Self report/JCEM	D, A	No	Cancer registry	√	√			√	None
Mills *et al.* (2005)	Nested case-control	Self report/JCEM	D	No	Cancer registry	√	√		√	√	None
Kogevinas *et al.* (1995)	Nested case-control	Self report/JEM	C	No	Cancer registry, death certificate	√	√			√	Latency analyses
Pahwa *et al.* (2012)	Population-based case control	Self/proxy report	D	No	Cancer registry /pathology review	√				√	None
Hohenadel *et al.* (2011)	Population-based case control	Self/proxy report	D	No	Cancer registry /pathology review	√				√	None
Miligi *et al.* (2006)	Population-based case control	Self report/CEM	D	No	Hospital records /pathology review	√	√			√	Restricted population
Hartge *et al.* (2005)	Population-based case control	Self report / measurement	D, concentration in carpet dust	Yes	Cancer registry	√	√			√	None

Lee *et al.* (2004)	Population-based case control	Self/proxy report	D	No	Cancer registry, hospital records	√	√				None
De Roos *et al.* (2003)	Population-based case control	Self/proxy report	D	No	Cancer registry, hospital record / pathology review	√			√	√	Different regression models
Miligi *et al.* (2003)	Population-based case control	Self report/CEM	D	No	Hospital records /pathology review	√				√	None
McDuffie *et al.* (2001)	Population-based case control	Self/proxy report	D, F	Yes	Cancer registry /pathology review	√				√	None
Hardell *et al.* (1994)	Population-based case control	Self/proxy report	D	No	Hospital records /pathology review	√	√			√	None
Cantor *et al.* (1992)	Population-based case control	Self/proxy report	D, handled without protective equipment	No	Cancer registry /pathology review	√		√		√	Noe
Zahm *et al.* (1990)	Population-based case control	Self/proxy report	D, F, TF, timing of change to clean clothes	Yes	Hospital records /pathology review	√			√		Restricted population
Weisenberger (1990)	Population-based case control	Self/proxy report	D, F	No	Hospital records /pathology review	√					None
Woods and Polissar (1989)	Population-based case control	Self/proxy report	D	No	Cancer registry	√				√	None
Hoar *et al.* (1986)	Population-based case control	Self or proxy report /supplier record	D, L, F, first year of use	No	Cancer registry /pathology review	√				√	None
Band *et al.* (2011)	Proportional registration study	Self/proxy report /JEM	D	No	Cancer registry	√				√	None

Mills (1998)	Ecological study	Municipal record	A	No	Cancer registry							None

Notes:

(a) JEM for job exposure matrix, JCEM for job/crop exposure matrix, CEM for crop exposure matrix.

(b) D for dichotomous 2,4-D exposure, L for duration, I for intensity, C for cumulative exposure, F for frequency, TF for time of first exposure, and A for amount.

(c) "Yes" indicates that results of a statistical test for dose-response were reported, either qualitatively or quantitatively (i.e. with a p-value).

(d) Consideration of confounders indicates that a covariate was either assessed for impact on risk estimates and/or included in final models as a covariate. "Other" confounders include geographic location/study site, respondent type (proxy vs. self), alcohol consumption, year, race, income, vital status, and general medical history.

Table 3 Summary RRs for NHL from Meta-analyses of All Studies and Subgroups

Subgroup Analysis	Study Characteristic	# of Studies	RR	95% CI	I^2	P for within-group heterogeneity	P for between-group heterogeneity
Primary analysis	None	9	0.97	0.77-1.22	28.8%	0.189	NA
Study design	Cohort/nested case-control	3	1.49	0.89-2.45	16.5%	0.302	0.07
	Population-based case control	6	0.86	0.71-1.04	0.0%	0.508	
Type of exposure	Exclusively agricultural	5	0.91	0.61-1.36	45.2%	0.140	0.38
	Other	3	1.06	0.79-1.36	11.2%	0.342	
Geographic location	US	5	0.99	0.70-1.41	48.4%	0.410	0.78
	Non-US	4	0.99	0.71-1.37	10.6%	0.340	
Sex	Male only	5	0.93	0.70-1.24	38.9%	0.162	0.67
	Male and female	4	1.10	0.70-1.73	28.6%	0.240	

Note:

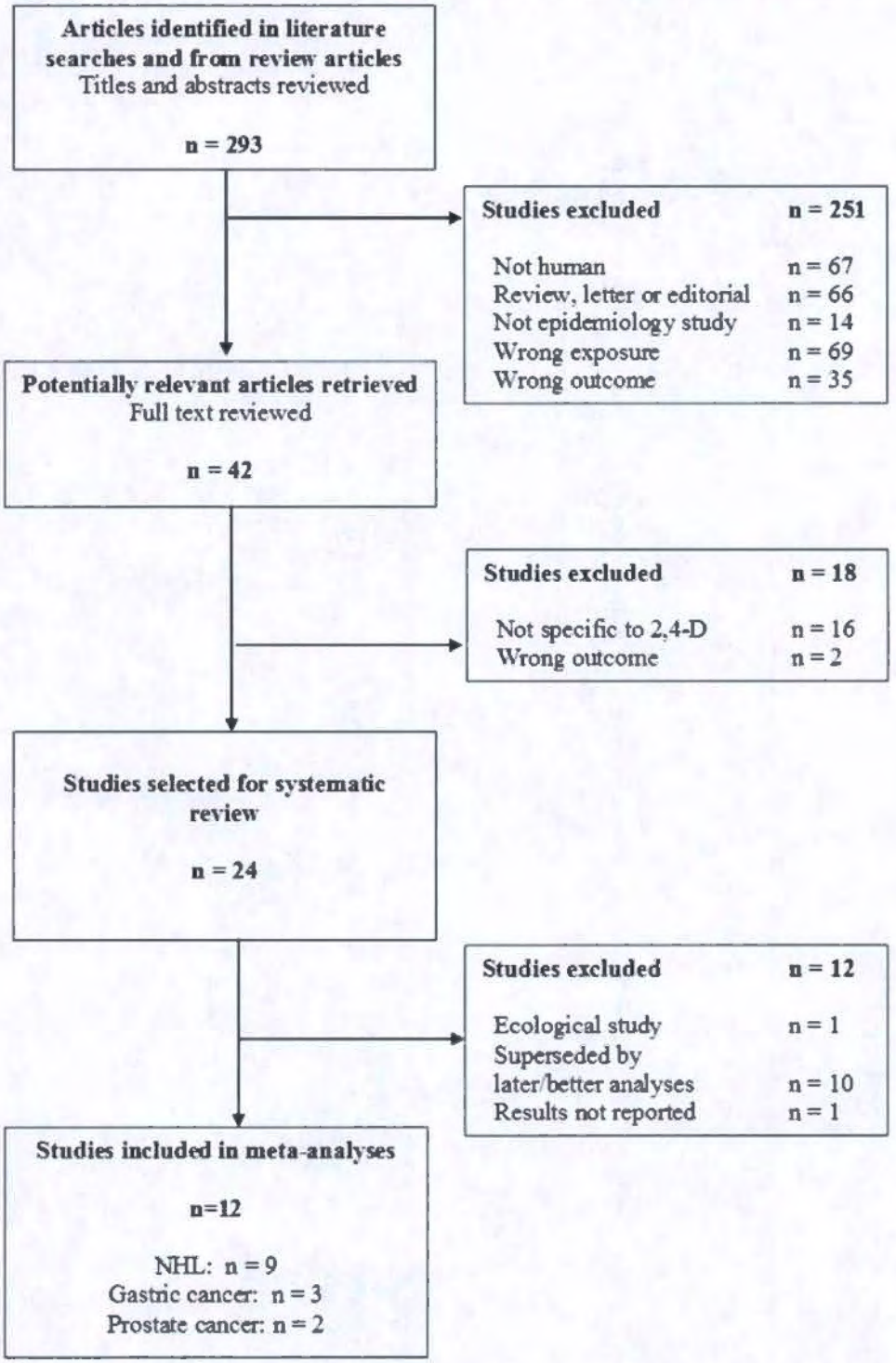
RR - relative risk; CI - confidence interval; NA - not avaliable.

Table 4 Summary RRs for NHL from Meta-analysis of All Studies and Sensitivity Analyses

Sensitivity Analyses	Description	# of Studies	RR	95% CI	I^2	P for heterogeneity
1	Results from De Roos et al. (2003) based on hierarchical regression instead of logistic regression used	9	1.00	0.80-1.24	20.3%	0.263
2	Pahwa et al. (2012) used instead of Hohenadel et al., (2011)	9	1.06	0.82-1.37	45.2%	0.067
3	Results from individual studies (Cantor, Hoar and Zahm) used in place of pooled De Roos et al. (2003) results	11	1.22	0.96-1.55	46.1%	0.046
4	Unadjusted effect estimate from Mills et al. (2005) used instead of estimate adjsuted for other pesticide exposure	9	1.10	0.80-1.51	62.0%	0.007
5	Combination of sensitivity analyses 2,3, and 4	11	1.34	1.04-1.72	56.3%	0.011
6	Woods and Polissar (1989) excluded	8	1.02	0.79-1.31	33.3%	0.162
	Mills et al. (2005) excluded	8	0.91	0.76-1.09	0.0%	0.455
	Miligi et al. (2006) excluded	8	1.00	0.77-1.29	37.6%	0.129
	Hohenadel et al. (2011) excluded	8	1.01	0.75-1.35	37.7%	0.129
	Burns et al. (2011) excluded	8	0.93	0.73-1.17	25.2%	0.228
	Hartge et al. (2005) excluded	8	1.00	0.77-1.30	37.5%	0.130
	Hardell et al. (1994) excluded	8	0.94	0.77-1.14	11.9%	0.337
	Kogevinas et al. (1995) excluded	8	0.97	0.76-1.25	36.8%	0.135
	De Roos et al. (2003) excluded	8	1.04	0.79-1.37	28.0%	0.204

Note:

RR - relative risk; CI - confidence interval.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Review, letter or editorial n = 66
Not epidemiology study n = 14
Wrong exposure n = 69
Wrong outcome n = 35
Potentially relevant articles retrieved
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Wrong outcome n = 2
Studies selected for systematic review
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Ecological study n = 1
Superseded by later/better analyses n = 10
Results not reported n = 1
Studies included in meta-analyses
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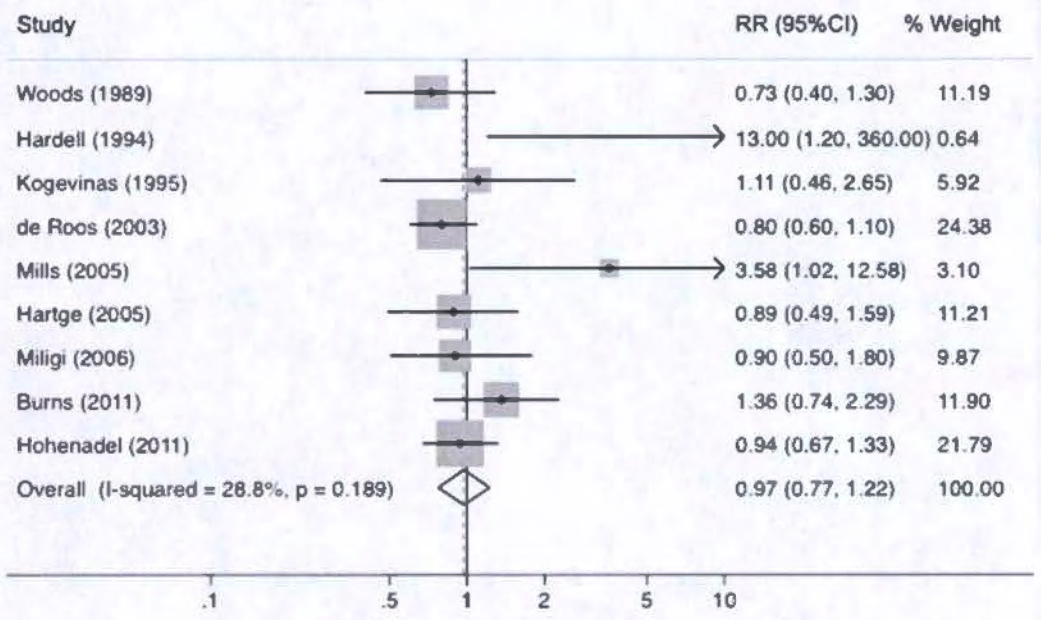
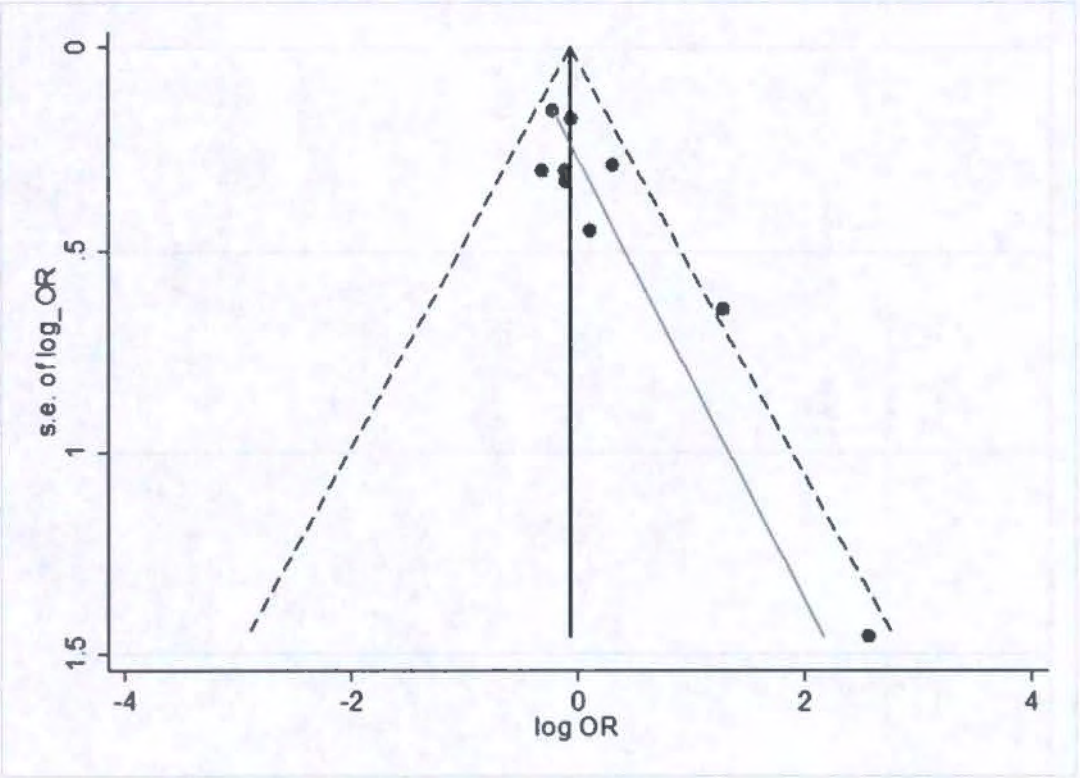
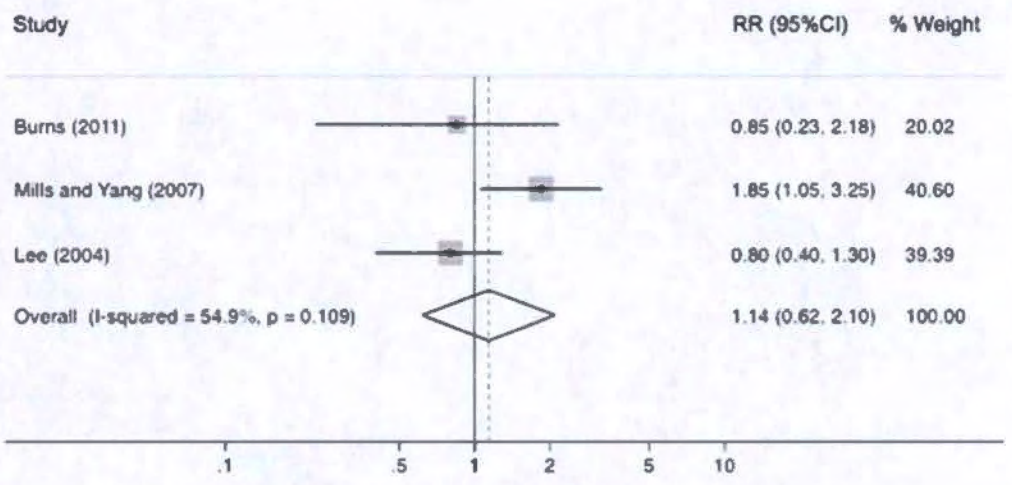
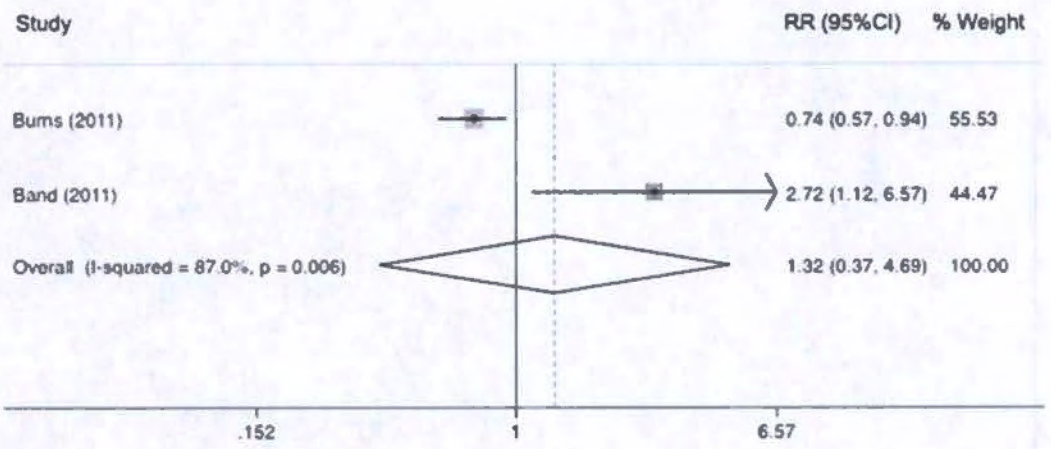
NHL: n = 9
Gastric cancer: n = 3
Prostate cancer: n = 2









Supplemental Table 1 Results of Studies Evaluating 2,4-D and NHL

Study	Exposure Metric	Exposure Category	Outcome Assessed	Stratum	# of Cases	Risk Estimate	Result	95% CI	P for Trend
Burns *et al.* (2011)	Employment	Yes	Total NHL		14	SIR	1.36	0.74-2.29	
	Duration of employment (years)	<1			7		1.08	0.43-2.22	0.12
		1-4.99			3		1.21	0.25-3.55	
		≥5			4		3.08	0.84-7.88	
	Cumulative exposure (exposure-years)	<1			9		1.24	0.57-2.36	0.46
		1-4.99			2		1.23	0.15-4.43	
		≥5			3		2.16	0.45-6.31	
Burns *et al.* (2001)	Exposure to 2,4-D	Yes	Total NHL		3	SMR	1	0.21-2.92	
	Exposure to 2,4-D, lagged 20 years	Yes			1		0.36	0.01-2.00	
	Exposure to 2,4-D	Yes			3	RR	2.63	0.85-8.33	
	Cumulative exposure (exposure-years)	<0.05			1		3.28		>0.05
		0.05-0.49			0		0		
		0.5-4.9			2		6.11		
		≥5			0		0		
	Cumulative exposure (exposure-years), lagged 20 years	<0.05			3		4.49		>0.05
		0.05-0.49			0		0		
		0.5-4.9			0		0		
		≥5			0		0		
Bloemen *et al.* (1993)	Exposure to 2,4-D	Yes	Total NHL		2	SMR	1.96	0.24-7.08	
	Exposure to 2,4-D				2	RR	3.03	0.78-11.85	
Pahwa *et al.* (2012)	Exposure to 2,4-D	Yes	Total NHL		110	OR	1.27	0.98-1.65	
Miligi *et al.* (2006)	Probability of exposure to 2,4-D	>low	Total NHL		17	OR	0.9	0.5-1.8	
	Exposure to 2,4-D	Probability of exposure >low and lack of protective equipment use			9		4.4	1.1-29.1	

Study	Exposure Metric	Exposure Category	Outcome Assessed	Stratum	# of Cases	Risk Estimate	Result	95% CI	P for Trend
Mills *et al.* (2005)	Exposure to 2,4-D	High	Total NHL		NR	OR	3.8	1.85-7.81	
			NHL-Nodal		NR		2.29	0.90-5.82	
			NHL-Extranodal		NR		9.73	2.68-35.3	
			Total NHL	Men	NR		3.79	1.58-9.11	
				Women	NR		5.23	1.30-20.9	
			Total NHL (adjusted for other pesticides)		NR		3.58	1.02-12.56	
McDuffie *et al.* (2001)	Exposure to 2,4-D	Yes	Total NHL		111	OR	1.32	1.01-1.73	
	Frequency of exposure (days/year)	Unexposed			406		1		NS
		> 0 and ≤2			55		1.17	0.83-1.64	
		>2 and ≤5			36		1.39	0.91-2.13	
		>5 and ≤7			9		1.38	0.60-3.15	
		>7			11		1.22	0.60-2.49	
Weisenberger (1990)	Exposure to 2,4-D	Yes	Total NHL		NR	OR	1.5	0.9-2.5	
Zahm *et al.* (1990)	Exposure to 2,4-D	Yes	Total NHL		43	OR	1.5	0.9-2.5	
	Frequency of exposure (days/year)	Never			54		1		0.051
		1-5			16		1.2	0.6-2.4	
		6-20			12		1.6	0.7-3.6	
		> 20			3		3.3	0.5-22.1	
		Unknown			12		NR		
	Duration of exposure (years)	Never			54		1		0.274
		1-5			3		0.9	0.2-3.6	
		6-15			11		2.8	1.1-7.1	
		16-20			3		0.6	0.1-2.1	
		> 20			13		1.3	0.6-2.7	
		Unknown			15		NR		

Study	Exposure Metric	Exposure Category	Outcome Assessed	Stratum	# of Cases	Risk Estimate	Result	95% CI	P for Trend
Zahm et al. (1990) cont'd	Year of first exposure	Never	Total NHL		54	OR, adjusted for age, organophosphates and fungicides	1		0.17
		Prior to 1945			8		1.4	0.5-3.5	
		1946-1955			13		1.1	0.5-2.3	
		1956-1965			5		2.1	0.6-7.7	
		1966-1986			4		1.3	0.3-4.9	
		Unknown			13		NR		
	Timing of change to clean clothes	Never exposed			54		1		0.015
		Immediately after handling pesticides			6		1.1	0.4-3.1	
		At the end of work day			31		1.5	0.8-2.6	
		Following day or later			6		4.7	1.1-21.5	
	Frequency of exposure (days/year)	Never			54		1		
		1-5			16		0.8	NR	
		6-20			12		1.3	NR	
		> 20			3		3.1	NR	
	Frequency of exposure (days/year)	Never		Farmers	NR	OR, adjusted for age, organophosphates and fungicides	1		
		> 20		Farmers	3		2.1	NR	
	Frequency of exposure (days/year)	Never		Proxy interview	NR	OR	1		
		1-5					2.2	NR	
		6-20					2.2	NR	
		> 20					2.4	NR	
		Never		Self-respondents	NR		1		
		1-5					1	NR	
		6-20					1.6	NR	
		>20					1.4	NR	

Study	Exposure Metric	Exposure Category	Outcome Assessed	Stratum	# of Cases	Risk Estimate	Result	95% CI	P for Trend
Zahm et al. (1990) cont'd	Exposure to 2,4-D	Ever	Intermediate grade NHL		NR	OR	1.7	NR	
		> 20 days/year			2		5		
		Ever	Follicular center cell NHL		NR		1.7	NR	
		> 20 days/year			2		6.4		
		Ever	Large cell NHL		NR		1.5	NR	
		>20 days/year			1		6.2		
		Ever	blastic NHL		NR		2.3	NR	
		>20 days/year			1		9.3		
		Ever	T-cell lymphoma		NR		2	0.5-7.3	
		Ever	B-cell lymphoma		NR		1.5	0.9-2.6	
	Frequency of exposure (days/year)	Never	B-cell lymphoma		NR	OR	1	NR	0.045
		1-5			NR		1.1		
		6-20			NR		1.6		
		>20			NR		4.3		
Woods and Polissar (1989)	Exposure to 2,4-D	Yes	Total NHL		NR	OR	0.73	0.4-1.3	
				Farmers	NR		0.68	0.3-1.4	
Hartge *et al.* (2005)	Concentration of 2,4-D in carpet dust (ng/g)	Below detection limit	Total NHL		147	OR	1		NS
		<500			257		1.1	0.78-1.55	
		500-999			86		0.91	0.58-1.45	
		1,000-9,999			165		0.66	0.45-0.98	
		>10,000			24		0.82	0.41-1.66	
	Exposure to 2,4-D	Low (no 2,4-D in carpet and reported no use)	Total NHL		60	OR	1		
		High (≥ 50 applications of herbicide with ≥ 1,000 ng/g 2,4-D in carpet)			NR		0.89	0.49-1.59	

Study	Exposure Metric	Exposure Category	Outcome Assessed	Stratum	# of Cases	Risk Estimate	Result	95% CI	P for Trend
Cantor *et al.* (1992)	Exposure to 2,4-D	Ever	Total NHL		115	OR	1.2	0.9-1.6	
		Handled prior to 1965			86	OR	1.3	0.9-1.8	
		Handled without protective equipment			89	OR	1.2	0.9-1.7	
		Handled prior to 1965		Iowa	51	OR	1.2	0.8-1.9	
		Handled prior to 1966		Minnesota	35	OR	1.4	0.9-2.3	
Hardell *et al.* (1994)	Exposure to 2,4-D	Yes	Total NHL		3	OR	13	1.2-360	
Hoar *et al.* (1986)	Exposure to 2,4-D	Yes	Total NHL		21	OR	2.6	1.4-5.0	
Mills (1998)	2,4-D use	Pounds of active ingredient	Total NHL	Male, white	NA	Pearson correlation coefficient	-0.2	NR p >0.05	
				Female, white			-0.28		
				Male, Hispanic			-0.24		
				Female, Hispanic			-0.01		
Kogevinas et al. (1995)	Cumulative exposure to 2,4-D	Yes, lagged 5 years	Total NHL		12	OR	1.11	0.46-2.65	
		Unexposed			20		1		
		Low			4		0.73	0.22-2.43	
		Medium			6		2.14	0.73-6.23	
		High			2		0.69	0.11-4.55	
Hohenadel *et al.* (2011)	Exposure to 2,4-D	Yes	Total NHL		49	OR	0.94	0.67-1.33	

Study	Exposure Metric	Exposure Category	Outcome Assessed	Stratum	# of Cases	Risk Estimate	Result	95% CI	P for Trend
De Roos *et al.* (2003)	Exposure to 2,4-D	Yes	Total NHL		123	OR, logistic regression	0.8	0.6-1.1	
						OR, hierarchical regression	0.9	0.6-1.2	
Miligi *et al.* (2003)	Probability of exposure to 2,4-D	> low	Total NHL	Men	6	OR	0.7	0.3-1.9	
				Women	7		1.5	0.4-5.7	

Notes:
CI - confidence interval; NHL - non-Hodgkin's lymphoma; 2,4-D - 2,4-dichlorophenoxyacetic acid; NR - not reported; NA - not available; NS - not significant; OR - odds ratio; SIR - standardized incidence ratio; SMR - standardized mortality ratio; RR - relative risk.

Supplemental Table 2 Results of Studies Evaluating 2,4-D and Gastric Cancer

Study	Exposure Metric	Exposure Category	Outcome Assessed	Stratum	# of Cases	Risk Estimate	Result	95% CI
Burns *et al.* (2011)	Employment	Yes	Stomach cancer		4	SIR	0.85	0.23-2.18
Mills and Yang (2007)	Exposure to 2,4-D	Ever	Gastric cancer		42	OR	1.85	1.05-3.25
	Amount of 2,4-D use (lbs)	0	Gastric cancer		58	OR	1	
		1-14			17	OR	2.16	1.02-4.56
		15-86			14	OR	1.57	0.71-3.51
		86-1,950			11	OR	2.09	0.87-5.05
		1-14	Gastric cancer		17	OR	1	
		15-86			14	OR	0.86	0.32-2.3
		86-1,950			11	OR	1.04	0.37-2.93
	Exposure to 2,4-D	Ever	Gastric cancer	Non-cardia	NR	OR	1.8	0.97-3.34
				Cardia	NR	OR	2.07	0.47-9.16
				Intestinal	NR	OR	1.89	1.00-3.58
				Diffuse	NR	OR	1.33	0.34-5.28
				Grade I and II	NR	OR	12.83	3.00-54.94
				Grade III and IV	NR	OR	1.13	0.58-2.19
Lee *et al.* (2004)	Exposure to 2,4-D	Ever	Stomach cancer		27	OR	0.8	0.4-1.3
Bond *et al.* (1988)	Exposure to 2,4-D	Yes	Stomach cancer		0	SMR	-	0-3.73
	Exposure to 2,4-D, lagged 15 years				0	SMR	-	0-5.37

Notes:
CI - confidence interval; 2,4-D - 2,4-dichlorophenoxyacetic acid; OR - odds ratio; NR - not reported; SIR - standardized incidence ratio.

Supplemental Table 3 Results of Studies Evaluating 2,4-D and Prostate Cancer

Study	Exposure Metric	Exposure Category	# of Cases	Risk Estimate	Result	95% CI	P for Risk Estimates
Burns *et al.* (2011)	Employment	Yes	62	SIR	0.74	0.57-0.94	
Burns *et al.* (2001)	Exposure to 2,4-D	Yes	7	SMR	1.34	0.54-2.77	
	Exposure to 2,4-D, lagged 20 years		5	SMR	1.07	0.35-2.50	
Alavanja *et al.* (2003)	Cumulative exposure	NR	NR	NR	NR	NR	>0.05
Band *et al.* (2011)	Exposure to 2,4-D	Ever	11	OR	2.72	1.12-6.57	
	Exposure to 2,4-DB	Ever	24	OR	1.77	1.04-3.03	
Bond *et al.* (1988)	Exposure to 2,4-D	Yes	1	SMR	1.04	1-5.76	
	Exposure to 2,4-D, lagged 15 years		0	SMR	-	0-4.33	

Notes:
CI - confidence interval; 2,4-D - 2,4-dichlorophenoxyacetic acid; 2,4-DB - 4-(2,4-dichlorophenoxy)butyric acid; NR - not reported; OR - odds ratio; SIR - standardized incidence ratio; SMR - standardized mortality ratio.